L10 ANSWER 17 OF 18 USPATFULL on STN
ACCESSION NUMBER: 1999:155775 USPATFULL
TITLE: Antipsychotic prodrugs comprising an antipsychotic agent coupled to an unsaturated fatty acid
INVENTOR(S): Shashoua, Victor E., Brookline, MA, United States
PATENT ASSIGNEE(S): Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5994392		19991130
APPLICATION INFO.:	US 1995-462820		19950605 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-80675, filed on 21 Jun 1993, now abandoned which is a continuation of Ser. No. US 1992-952191, filed on 28 Sep 1992, now abandoned which is a continuation of Ser. No. US 1990-577329, filed on 4 Sep 1990, now abandoned which is a continuation-in-part of Ser. No. US 1990-535812, filed on 11 Jun 1990, now abandoned which is a continuation of Ser. No. US 1989-315134, filed on 24 Feb 1989, now patented, Pat. No. US 4933324 which is a continuation-in-part of Ser. No. US 1988-160667, filed on 26 Feb 1988, now patented, Pat. No. US 4939174
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Geist, Gary
ASSISTANT EXAMINER: Carr, Deborah D.
LEGAL REPRESENTATIVE: Wolf, Greenfield & Sacks, P.C.
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1475
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . muscle relaxants, anti-parkinson agents, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents, local anesthetics, anti-spasmodics and muscle contractants, prostaglandins, anti-bacterials, anti-septics, anti-depressants, anti-**migraine** preparations, central nervous system stimulants, im

L10 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:300478 CAPLUS
DOCUMENT NUMBER: 134:316117
TITLE: Sustained-release formulations for treating CNS-mediated disorders
INVENTOR(S): Wells, David S.; Marriott, Thomas B.; Rajewski, Lian G.; Pipkin, James D.; Haslam, John L.
PATENT ASSIGNEE(S): Nps Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001028516	A2	20010426	WO 2000-US41267	20001019
WO 2001028516	A3	20020221		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2387819	AA	20010426	CA 2000-2387819	20001019
EP 1225888	A2	20020731	EP 2000-982701	20001019
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003512311	T2	20030402	JP 2001-531111	20001019
PRIORITY APPLN. INFO.:			US 1999-160210P	A2 19991019
			WO 2000-US41267	W 20001019

OTHER SOURCE(S): MARPAT 134:316117

L10 ANSWER 1 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2004:308192 USPATFULL
TITLE: 5-acylamino-1,1'-biphenyl-4-carboxamide derivatives and
their use as p38 kinase inhibitors
INVENTOR(S): Angell, Richard Martyn, London, UNITED KINGDOM
Aston, Nicola Mary, Stevenage, UNITED KINGDOM
Bamborough, Paul, Stevenage, UNITED KINGDOM
Bamford, Mark James, Harlow, UNITED KINGDOM
Cockerhill, George Stuart, London, UNITED KINGDOM
Flack, Stephen Sean, London, UNITED KINGDOM
Laine, Dramane Ibrahim, Stevenage, UNITED KINGDOM
Merrick, Suzanne Joy, Stevenage, UNITED KINGDOM
Smith, Kathryn Jane, Stevenage, UNITED KINGDOM
Walker, Ann Louise, Stevenage, UNITED KINGDOM

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004242868	A1	20041202	
APPLICATION INFO.:	US 2004-492605	A1	20040415	(10)
	WO 2002-EP11576		20021016	

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2001-24939	20011017

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY, GLAXOSMITHKLINE, FIVE MOORE DR., PO BOX 13398, RESEARCH
TRIANGLE PARK, NC, 27709-3398
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 2451
SUMM . . . a human or animal subject suffering from any type of pain including chronic pain, rapid onset of analgesis, neuromuscular pain, **headache**, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and **migraine** pain which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically. . .
SUMM . . . of a medicament for the treatment of any type of pain including
chronic pain, rapid onset of analgesis, neuromuscular pain, **headache**, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and **migraine** pain.
DETD N-(4'-{[(Cyclopropylmethyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)
isovaleramide
DETD . . . and the combined filtrate and washings filtered through an SPE (SCX), to give, after evaporation of the solvent under vacuum, N-(4'-{[(cyclopropylmethyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)

isovaleramide. NMR; .delta.H [.sup.2H.sub.6]--DMSO 9.84,(1H, s), 8.60,(1H, t), 7.91,(2H, d), 7.50-7.48,(2H, m), 7.40,(2H, d), 7.21,(1H, d), 3.16,(2H, t), 2.16-2.15,(5H, m), 2.06,(1H,. . .

L10 ANSWER 2 OF 18 USPATFULL on STN

ACCESSION NUMBER:	2004:95445 USPATFULL
TITLE:	Treating a variety of pathological conditions, including **spasticity** and convulsions, by effecting a modulation of CNS activity with **isovaleramide**, isovaleric acid, or a related compound
INVENTOR(S):	Artman, Linda D., Salt Lake City, UT, UNITED STATES Balandrin, Manuel, Sandy, UT, UNITED STATES Smith, Robert L., Lansdale, PA, UNITED STATES
PATENT ASSIGNEE(S):	NPS PHARMACEUTICALS (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004072900	A1	20040415
APPLICATION INFO.:	US 2003-614344	A1	20030708 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-258882, filed on 1 Mar 1999, GRANTED, Pat. No. US 6589994
Continuation-in-part
of Ser. No. WO 1997-US15272, filed on 29 Aug 1997, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-25050P	19960830 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	FOLEY AND LARDNER, SUITE 500, 3000 K STREET NW, WASHINGTON, DC, 20007
NUMBER OF CLAIMS:	32
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	7 Drawing Page(s)
LINE COUNT:	1615

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Treating a variety of pathological conditions, including **spasticity** and convulsions, by effecting a modulation of CNS activity with **isovaleramide**, isovaleric acid, or a related compound

AB Preparations and extracts of valerian, as well as **isovaleramide**, isovaleric acid, and certain structurally related compounds exhibit clinically significant pharmacological properties which implicate a treatment for a variety of pathological conditions, including **spasticity** and convulsions, which are ameliorated by effecting a modulation of CNS activity. The compositions in question generally are non-cytotoxic and. . .

SUMM [0002] The present invention provides methods of treating pathological conditions, such as **spasticity** and convulsions, the symptoms of which are alleviated by a modulation of activity in the central nervous system (CNS), without. . . excessive sedation or muscle weakness in animal subjects, including humans. More particularly, the invention relates to the therapeutic use of **isovaleramide**, isovaleric acid, and related compounds in patients suffering from pathologies of this nature.

SUMM . . . disorders are characterized by a profound aberration in the

normal function of the central nervous system (CNS). Such conditions include **spasticity**, strokes, spinal cord injuries, chronic neurodegenerative disorders and diseases such as Parkinson's and Huntington's diseases, Alzheimer's disease, and epilepsy. At. . .

SUMM [0004] Many agents currently employed in the treatment of pathologies such as **spasticity** and convulsions display troubling side-effect profiles which limit their long-term clinical utility. Among these agents, for example, are the benzodiazepines,. . . These side-effects severely limit the therapeutic potential for both drugs. It is apparent, therefore that improved and better-tolerated treatments for **spasticity**, convulsions, and other therapeutic indications are greatly to be desired.

SUMM . . . of the present invention to provide a method for alleviating one or more symptoms associated with a condition, such as **spasticity**, that is ameliorated by means of a centrally mediated decrease in muscle tone.

SUMM [0008] It is another object of the present invention to provide a novel prophylactic therapy for **migraine** and other **headache** pathologies.

SUMM . . . according to one aspect of the present invention, a method of using a compound selected from the group consisting of **isovaleramide**, a pharmaceutically acceptable ester of isovaleric acid, a pharmaceutically acceptable amide of isovaleric acid, and a compound selected from the group consisting of 2-methyl **isovaleramide**, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-**isovaleramide**, 2-hydroxyisovaleramide, N-(2-acetamido)**isovaleramide**, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate.

SUMM . . . to one embodiment of the invention, the pharmaceutically acceptable amide of isovaleric acid is selected from the group consisting of **isovaleramide**, N-ethyl **isovaleramide**, N-methyl **isovaleramide**, N,N-dimethyl **isovaleramide**, N-methyl,N-ethyl **isovaleramide**, N-(2-acetamido) **isovaleramide** ("N-isovaleryl glycinamide"), and N-isovaleryl GABA.

SUMM . . . another embodiment of the invention, the treated pathology is an affective mood disorder, convulsions, a central neuropathic pain syndrome, a **headache**, or a restlessness syndrome. In still another embodiment, the pathology is **spasticity** that is ameliorated by a centrally mediated decrease in muscle tone. In a further embodiment, the treated pathology is a. . .

SUMM . . . provided for an extract of Valerianaceae, cramp bark, black haw, or hops in a method of treating a symptom of **spasticity**, where the extract comprises at least one compound that is hydrolyzed in vivo to yield isovaleric acid or **isovaleramide**. By the same token, the present invention provides a method for alleviating a symptom of **spasticity** in a subject in need of such treatment, comprising the step of administering a therapeutically effective amount of an extract. . .

DRWD [0018] FIGS. 1a and 1b depicts the structures of compounds, including

isovaleramide, capable of inducing a modulation of the central nervous system.

DRWD [0019] FIG. 2 portrays the effect of **isovaleramide** (at 300 mg/kg, i.p.) on gross observational **spasticity** scores elicited by a metal probe applied to the abdomen in the chronic spinalized rat. Each rat served as its. . .

DRWD [0020] FIG. 3 illustrates a time-dependent reduction of the flexor reflex, an electrophysiological measure of **spasticity**, in the chronic spinalized rat. The effects of **isovaleramide** (300 mg/kg p.o.), baclofen (10 mg/kg s.c.), and vehicle (water, 12 ml/kg p.o.) are shown at pre-treatment (time zero) and at 30, 60, 90, and 120 minutes post-administration. **Isovaleramide** caused a significant decrease in the magnitude of the flexor reflex, comparable to that observed with baclofen.

DRWD [0021] FIG. 4 shows a dose-response relationship for **isovaleramide** and baclofen, a known antispasticity agent. **Isovaleramide** and baclofen produced a similar dose-dependent reduction of the flexor reflex in the chronic spinalized rat. The responses from FIG.. . .

DRWD [0022] FIG. 5 shows that **isovaleramide** was effective in reducing in a dose-dependent manner the generalized seizure responses of fully kindled rats. **Isovaleramide** decreased the mean seizure score and the afterdischarge duration in amygdala-kindled rats, showing that it exerts anticonvulsant activity against both. . .

DRWD [0023] FIG. 6 illustrates the antiepileptogenesis effect of a daily 500 mg/kg p.o. dose of **isovaleramide** compared to controls. **Isovaleramide** elicited a delay in the rate of increase in both seizure score and afterdischarge duration (not shown) which normally develop. . .

DETD [0025] Isovaleric acid and its pharmaceutically acceptable salts, amides such as **isovaleramide**, and alcohol esters such as ethyl isovalerate and glyceryl triisovalerate can be administered in vivo to effect a modulation of. . . or no accompanying paralysis), eliciting a calmative effect (with little or no sedation), or ameliorating an ambulatory syndrome such as **spasticity** (with little or no accompanying weakness or flaccidity).

DETD [0026] A number of pathologies, exemplified by affective mood disorders (i.e. bipolar disorder), headaches (chronic, cluster, **migraine**), restlessness syndromes, neuropathic pain, movement disorders, **spasticity**, convulsions, cerebral insult, neurodegeneration, and substance abuse have at least one symptom that is usefully alleviated by effecting a modulation. . . pathology may be treated with a therapy where, pursuant to the present invention, that individual receives a pharmaceutical formulation of **isovaleramide**, isovaleric acid, or a related compound.

DETD [0031] **SPASTICITY: Spasticity** may be "defined as an upper [i.e., CNS] motor neuron disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex." Lance, Symposia synopsis in **SPASTICITY**--DISORDERED MOTOR CONTROL, Feldman et al. (eds.) (1980) (Symposia Specialists, distributed by Year Book Medical Publishers). An increase in tonic stretch. . .

DETD [0032] Major disease states and conditions associated with **spasticity** include multiple sclerosis, cerebral palsy, stroke, trauma or injury to the spinal cord, and closed head trauma. There are "positive symptoms" that can occur with **spasticity**, such as the Babinski response, painful flexor or extensor spasms, increased or exaggerated deep tendon reflexes, and clonus. Other symptoms,. . . paresis" (spastic paralysis). Pain, impairment of sleep, and various degrees of loss of general motor function are also associated with **spasticity**.

DETD [0033] The pathological states observed in **spasticity** are fundamentally different at the physiological level from the commonly experienced acute muscular aches, strains, and sprains that occur from. . . or localized symptoms are commonly treated with so-called "antispasmodic" or "spasmolytic" agents. Such agents generally are not useful in treating **spasticity**. Cedarbaum & Schleifer, "Drugs for Parkinson's Disease, **Spasticity** and Acute Muscle Spasms," in GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 8th ed. [hereafter GOODMAN AND GILMAN'S], pages. . .

DETD . . . decrease in muscle tone and, hence, are useful for the acute or chronic alleviation of one or more symptoms of **spasticity**. In the context of the present invention, "**spasticity**" refers to a heightened tone of skeletal muscle which is manifested by symptoms exemplified by but not limited to painful. . . jerks, and clonus. The phrase "antispasticity agent" refers here to a composition that is useful for the symptomatic treatment of **spasticity**, as demonstrated by the alleviation of at least one of the following manifestations of **spasticity**: painful flexor or extensor spasms, increased or exaggerated deep tendon reflexes, hyperreflexia, loss of dexterity, muscular weakness, exaggerated tendon jerks, and clonus. Accordingly, the "alleviation" of **spasticity** refers here to the lessening of one or more symptoms of **spasticity**, including, but not limited to, painful flexor or extensor spasms, increased or exaggerated deep tendon reflexes, hyperreflexia, loss of dexterity,. . .

DETD [0035] **Spasticity** is associated with multiple sclerosis, stroke, head trauma, spinal cord injuries, cerebral palsy, and other neurodegenerative diseases, disorders, and conditions. **Spasticity** is distinct from acute muscle spasms, which may be associated with a variety of conditions different from those leading to **spasticity**. These acute muscle spasm-causing conditions include trauma, inflammation, anxiety, and/or pain.

DETD [0036] The difference between **spasticity** and acute muscle spasms is illustrated by the fact that agents useful for the treatment of muscle spasms are not useful for treating **spasticity** associated with chronic neurological diseases. Cedarbaum & Schleifer (1990), supra. Likewise, agents used heretofore to treat **spasticity** associated with chronic neurological disorders have not been employed in treating acute muscle spasms, except for the benzodiazepines, such as. . . contrast, the present invention achieves a centrally mediated decrease in muscle tone which, in turn, addresses the particular symptoms of **spasticity**.

DETD . . . to the present invention is effective to this end, especially with respect to improved side effects. It is anticipated that **isovaleramide** and related compounds will demonstrate an absence of the type of side effects that significantly detract from the clinical

usefulness. . .

DETD [0045] HEADACHES: Headaches of the **migraine** type (Hering & Kuritzky, Cephalalgia 12: 81-84 (1992)), the cluster type (Hering & Kuritzky, loc. cit. 9: 195-98 (1989)) and the chronic type (Mathew & Sabiha, **Headache** 31: 71-74 (1991)) have been treated by the administration of valproate and other anticonvulsants. The compositions of the present invention also will alleviate symptoms associated with each of the three **headache** types, without the adverse side effects of valproate and other anticonvulsant therapy.

DETD . . . aqueous or hydroalcoholic extracts or tinctures, has been determined to be the ester hydrolysis product, isovaleric acid. Ammonium isovalerate and **isovaleramide** are produced in ammoniated tinctures. Balandrin et al., J. Toxicol.-Toxin Rev. 14: 165 (1995). The structures of **isovaleramide** and related compounds are depicted in FIG. 1. In this way, the chemically labile valepotriates and other valerian-derived monoterpenoid-isovalerate esters,. . . lavandulyl, and ethyl isovalerates, might be considered to act as "pro-drugs" and chemical precursors for isovaleric acid, its salts, and **isovaleramide**.

DETD [0063] **Isovaleramide** has been isolated from valerian plants, most probably as an isolation artifact following treatment with ammonia. Buckova et al., Cesk.. . . 88: 86063z (1978); see also Bos et al. and Fuzzati et al., Phytochem. Anal. 7: 143, 76 (1996). More recently, **isovaleramide** was shown to exhibit low acute toxicity in vivo, no mutagenic potential, and clinically useful anxiolytic properties (U.S. Pat. No. 5,506,268; PCT application WO 94/28,888). Methods for preparing **isovaleramide** are well known.

DETD [0064] Extracts of medicinal plants that are useful for treating the symptoms of **spasticity** can be prepared by aqueous, hydroalcoholic, or alcoholic extraction, or by extraction with other suitable solvents using methods well known. . . the present invention, useful extracts contain at least one of the following: isovaleric acid, its salts or complexes, ethyl isovalerate, **isovaleramide**, N-ethyl **isovaleramide**, and their chemical precursors. Useful extracts also share the common property of releasing isovaleric acid and/or **isovaleramide** upon hydrolysis in vivo. Standard methods for preparing such extracts can be found in pre-1950 editions of the U.S. PHARMACOPOEIA. . .

DETD [0071] In addition to **isovaleramide**, various N-substituted amides of isovaleric acid may be used in the inventive methods. These amides can be prepared by methods. . . example, March, ADVANCED ORGANIC CHEMISTRY: REACTIONS, MECHANISMS, AND STRUCTURE, 4th ed. (John Wiley and Sons 1992). Preferred amides include N-ethyl **isovaleramide**, N-methyl **isovaleramide**, N, N-dimethyl **isovaleramide**, N-methyl,N-ethyl **isovaleramide**, N-(2-acetamido)**isovaleramide** ("N-isovaleryl glycinamide"), and N-isovaleryl GABA. See, for example, Tanaka et al., J. Biol. Chem. 242: 2966 (1967).

DETD . . . present invention also is directed to compounds and methods of using compounds that, by virtue of their structural similarity to **isovaleramide**, share similar pharmacological activities. These compounds generally share the common structure: ##STR1##

DETD . . . FIGS. 1a and 1b and include substituted isovaleramides such as 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide,

2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-**isovaleramide**, 2-hydroxyisovaleramide, and 2,2-dimethyl-n-butyramide. For each of these compounds that contains one or more asymmetric centers, the present invention specifically includes.

. .

DETD [0080] N,N-Diethyl **isovaleramide** ("Valyl"), although purported to possess CNS depressant (sedative) activity, recently has been shown to possess CNS stimulant (convulsant) properties; see. . . of the isovalerate esters, these substituted amides should be hydrolyzed in vivo (in this case, via hepatic amidase enzymes), releasing **isovaleramide** or isovaleric acid.

DETD . . . present invention also is directed to certain sulfonamide, sulfamate, and carbamate compounds that, by virtue of their structural similarity to **isovaleramide**, share similar pharmacological activities. Preferred sulfonamides and sulfamates include 2-methyl-1-propylsulfonamide, 1-methylethyl sulfamate, and 2-methyl-1-propyl sulfamate. Preferred carbamates include isobutylcarbamate (CH.sub.3).sub.2CHCH.sub.2OCONH.sub.2). . .

DETD [0082] Certain of the compounds and preparations discussed above represent alternative forms for delivering isovaleric acid or **isovaleramide** in vivo. In cases such as isovaleryl salicylate and ethyl isovalerate, the pharmacologically active moiety corresponding to the alcohol portion. . . expected to exhibit a "Tylenol.RTM.-like" effect, similar to acetaminophen as well as the effect expected from the isovaleric acid or **isovaleramide** moiety. Such novel chemical combinations of a previously known, pharmacologically active alcohol, phenol, or primary or secondary amine with isovaleric. . .

DETD . . . example, in Green, "Protective Groups in Organic Synthesis", Wiley (1981), prior to preparation of the acid chloride. 2-hydroxy and 3-hydroxy **isovaleramide** are metabolites of **isovaleramide** in vivo, and can be isolated in high yield from the urine of a patient being treated with **isovaleramide**.

DETD . . . agent is physiologically significant if the presence of the agent results in the alleviation of one or more symptoms of **spasticity**, while an anticonvulsant agent is physiologically significant if the presence of the agent results in the reduction of the severity,. . .

DETD [0091] **Isovaleramide** and related compounds can be administered orally using solid oral dosage forms such as enteric-coated tablets, caplets, gelcaps, or capsules, or via liquid oral dosage forms such as syrups or elixirs. The indicated dosage of **isovaleramide** and related compounds as antispasticity agents is on the order of 50-1200 mg per dose or 1-20 mg/kg body weight.. . . in the form of drops (with a dropper from a "concentrate" preparation) for oral administration. In addition, compounds such as **isovaleramide** may be formulated into chewing gum to facilitate oral delivery and absorption.

DETD [0092] Alternatively, **isovaleramide** and related compounds can be administered by injection or other systemic routes, such as IV,

transdermal or transmucosal administration, for. . .

DETD [0093] In addition to a use in humans, **isovaleramide** and related compounds can be used, for example, as antispasticity agents or anticonvulsant agents, in animals such as cats, dogs,. . . administration via suppositories), or orally by addition to food or drink. As an antispasticity agent, the indicated oral dosage of **isovaleramide** and/or related compounds per kilogram of body weight of such animals is about 50-1200 mg/kg, depending upon the species of. . .

DETD [0094] The indicated oral dosage of **isovaleramide** and/or related compounds per kilogram body weight as anticonvulsant agents for animals is in the range of about 50-1200 mg/kg,. . .

DETD [0095] The present invention thus contemplates a variety of pharmaceutical compositions containing the active compounds described above (including **isovaleramide**, isovaleric acid, and/or its pharmaceutically acceptable salts, substituted amides, alcohol esters, sulfonamide, sulfamate, and carbamate analogs) as active ingredients that. . . pharmaceutical formulations which are outside the scope of the present invention, the common feature of the present formulations is that **isovaleramide**, isovaleric acid, and/or its pharmaceutically acceptable salts, substituted amides, alcohol esters, and sulfonate, sulfamate, and carbamate analogs, are present in. . .

DETD [0096] It is further understood that **isovaleramide** and/or related compounds can be used in combination with other pharmaceutically active ingredients.

DETD [0100] The mutant spastic mouse is a homozygous mouse that carries an autosomal recessive trait of genetic **spasticity**. The mouse is normal at birth, and then the mouse develops a coarse tremor, abnormal gait, skeletal muscle rigidity, and. . . or synthesis of GABA, such as valproate and the benzodiazepines, are effective compounds to ameliorate some of the symptoms of **spasticity** in this model, as well as in humans.

DETD [0101] The assessment of **spasticity** in the mutant spastic mouse can be performed by electrophysiological assessment similar to the EMG recordings described below. One can. . .

DETD [0103] There are several models of **spasticity** including the acute decerebrate rat, the acute or chronic spinally transected rat, and the chronically spinal cord-lesioned rat. (Wright, J.,. . . Clin Orthop 253:12, 1990). The acute models, although of proven value in elucidating the mechanisms involved in the development of **spasticity**, have come under criticism due to the fact that they are acute. The animals usually die or have total recovery from **spasticity**. The **spasticity** develops immediately upon intervention, unlike the **spasticity** that evolves in the human condition of **spasticity**, which most often initially manifests itself as a flaccid paralysis. Only after weeks and months does **spasticity** develop in humans. Some of the more chronic-lesioned or spinally transected models of **spasticity** do postoperatively show flaccid paralysis. At approximately four weeks post-lesion/transection, the flaccidity changes to **spasticity** of variable severity. Although all of these models have their own particular disadvantages and lack of true representation of the human spastic condition, they have provided much information about the nature

of **spasticity**. These models have also provided methods to test various treatment paradigms that have led to similar treatments being tested in. . .

DETD [0116] Neurogenic inflammation within the meninges has been proposed as an event in the underlying pathology of **migraine** headaches. Lee et al., Brit. J. Pharmacol. 116: 1661-67 (1995). Compounds are tested for their ability to block the leakage. . .

DETD [0127] The therapeutic effects of **isovaleramide**, isovaleric acid, and related compounds in various of the assays described above, combined with a general lack of toxicity, make the compounds of the present invention ideal agents for the treatment of the pathologies described above, including **spasticity** and convulsions/seizures. With this background, the present invention will be understood more readily by reference to the following examples, which. . .

DETD Use of a Valerian Preparation to Alleviate Symptoms of **Spasticity** Associated with Multiple Sclerosis

DETD Use of a Valerian Preparation to Alleviate Symptoms of **Spasticity** Associated with Spinal Cord Injury

DETD [0130] A human male subject, age 38, suffers symptoms of **spasticity** (hyperreflexia, tendon jerks, and extensor spasms) that evolved from an earlier injury to the spinal cord. All of these symptoms. . .

DETD **Isovaleramide** Antispasticity Tests

DETD [0131] (1) Assessment of **Spasticity** in Chronic Spinally Transected Rats

DETD . . . all animals regained bladder control and were no longer given antibiotic treatment. Advokat, Brain Res. 684: 8 (1995). Assessment of **spasticity** was performed before and after drug treatment such that each animal served as its own control.

DETD [0137] Initial assessment of **spasticity** was performed by the subjective scoring method of rating the resulting **spasticity** response elicited with an innocuous stimulus, i.e., a metal probe, that was pressed against the lower abdomen at four specific. . . zero (no spastic response in all four trials) to four (a maximum, tonic-clonic reaction elicited in all four trials). All **spasticity** scores, pre- and post-treatment, were transformed to indicate the percent **spasticity** such that a score of 0/4=0%, 1/4=25%, etc. These raw or normalized scores were analyzed with a one-way repeated measures. . .

DETD [0138] As shown in FIG. 2, **isovaleramide** at a dose of 300 mg/kg, i.p., was efficacious at 15, 30, 60, and 120 minutes post-administration in reducing the **spasticity** scores (45-65%). By the next day, i.e., by 1440 minutes (24 hours), the **spasticity** scores had essentially returned to baseline values. No overt behavioral toxicity or motor impairment was observed at this dose. The. . .

DETD . . . the flexor-reflex response (FIG. 3) before treatment and at each of 30, 60, 90, and 120 minutes following administration of **isovaleramide** (300 mg/kg p.o.), baclofen (10 mg/kg s.c.) and vehicle (water, 12 ml/kg p.o.), respectively.

DETD [0141] **Isovaleramide** was shown to reduce the magnitude of the flexor-reflex responses, at all time points in a chronic spinalized rat with. . .

DETD [0142] In FIG. 4, the responses from FIG. 3 and additional doses of **isovaleramide** and baclofen are converted to a total-area-under-the-curve format, covering the entire, two-hour measurement period. All drug-treated groups differed significantly from.

DETD [0144] Administered i.p. in the rat, **isovaleramide** induced no changes from saline-injected controls at doses up to 256 mg/kg. At 512 mg/kg, slight sedation from 60 to. . .

DETD [0146] **Isovaleramide**, administered at doses of 128, 256, and 512 mg/kg (i.p.) 60 minutes before a test on the rotarod, did not. . .

significantly affect rotarod performance in the rat. See Table 1. In contrast, diazepam dose-dependently decreased rotarod performance.

TABLE 1

Effects of **Isovaleramide** and Diazepam in the Rotarod Test in the Rat

Dose of: **Isovaleramide** (mg/kg).sup.a	Number.sup.b of Rats Falling	Drop-Off Time (sec) Mean .+-. S.E.M.	t value	% change from control
0	5	135.5 .+-. 18.0.sup.	--	--
128	6	134.5. . .		

DETD [0147] **Isovaleramide**, administered at doses up to 512 mg/kg (i.p.) 15 minutes before a test on the rotarod in the Frings mouse,. . .

DETD [0148] The results of Table 2 demonstrate the anticonvulsant activity of **isovaleramide** when administered i.p. in this animal model of epilepsy. **Isovaleramide** also displayed a quick onset and a relatively short duration of action. Anticonvulsant activity was noted as early as 15. . . was observed at this time point. At doses markedly higher than those providing anticonvulsant activity (>300 mg/kg), animals treated with **isovaleramide** displayed behavioral toxicity that was characterized by their inability to maintain their balance on the rotarod. No notable toxicity was. . .

DETD [0149] Therefore, despite the relatively low potency of **isovaleramide** in this model, it still displayed a relatively good separation between activity and toxicity. **Isovaleramide** thus had a surprising and unexpected efficacy, based on existing structure-activity relationships for amides and their corresponding acids, as an anticonvulsant in the Frings audiogenic seizure-susceptible mouse model of reflex epilepsy. The activity profile of **isovaleramide** is similar to that of the broad-spectrum anticonvulsant, sodium valproate. Compounds similar in structure to valproate as well as isovaleric. . . Keane et al., loc. cit. 22: 875 (1983); Keane et al., Pharmacol. Res. Commun. 17: 547 (1985).

TABLE 2

Effect of **Isovaleramide** on the Audiogenic Seizure Susceptibility of Frings Mice Following Intraperitoneal Administration

Dose of **Isovaleramide** (mg/kg, i.p.)	Seizure Score .+-. S.E.M.	Number.sup.a Protected of Eight Mice Tested	Number.sup.a Showing Toxicity of Eight Mice Tested
75	4.4 .+-. 0.6	1	0
112.5	4.0 .+-.. . .		

DETD [0150] The results of Table 3 demonstrate that **isovaleramide** displayed anticonvulsant activity when administered orally in this

animal model of epilepsy.

TABLE 3

Effect of **Isovaleramide** on the Audiogenic Seizure Susceptibility of Frings Mice Following Oral Administration

Dose of	Seizure	Number.sup.a Protected of Eight	Number.sup.c Showing Toxicity of. . .

DETD [0151] The results of Table 4 and Table 5 demonstrate that the **isovaleramide** analogs N-(2-acetamido)**isovaleramide** and 2-methylisovaleramide displayed anticonvulsant activity when administered orally in this animal model of epilepsy.

TABLE 4

Effect of N-(2-acetamido) **isovaleramide** on the Audiogenic Seizure Susceptibility of Frings Mice Following Oral Administration

Dose of N-(2-acetamido)	Number.sup.a Protected	Number.sup.a Protected	Number.sup.a Showing Toxicity. . .	Number.sup.a Showing

DETD . . . the structure-activity relationships of anticonvulsant activity around compounds similar to valproate have taught away from simple, unsubstituted compounds such as **isovaleramide**. It is thus a surprising and unexpected observation that **isovaleramide** has demonstrated an efficacy profile similar to that of valproate in the Frings audiogenic seizure-susceptible mouse model and a similar separation of activity between efficacy and toxicity as measured by rotarod performance. These observations indicate that **isovaleramide** is an effective therapeutic agent as a broad-spectrum anticonvulsant. **Isovaleramide** is known for its relative lack of toxicity in mutagenicity and cytotoxicity tests. See U.S. Pat. No. 5,506,268 and PCT. . .

DETD [0154] **Isovaleramide** was evaluated for its ability to block the expression of amygdala-kindled seizures in fully kindled rats. **Isovaleramide** was evaluated for its ability to block the kindled motor seizure (seizure scores of 4 and 5) and limbic behavioral. . .

DETD . . . ms biphasic 150 uA pulses that were delivered once daily until 10 consecutive stage 5 seizures were evoked. Testing of **isovaleramide** was initiated after a one-week, stimulus-free period. On the compound test day, rats displaying a stage 5 seizure were divided into multiple treatment groups (i.e. vehicle control and **isovaleramide** treatment). Sixty minutes after oral dosing, individual rats received a 300 uA, 1 sec duration stimulation and their seizure score. . .

DETD [0156] **Isovaleramide** was effective in reducing in a dose-dependent manner the generalized seizure responses of fully kindled rats. **Isovaleramide** decreased the mean seizure score and the afterdischarge duration showing that it exerts anticonvulsant activity against both focal (seizure score. . .

DETD . . . following coordinates with Bregma as zero: AP-2.2 mm, ML-4.7

mm, DV-8.7 mm. Chronic treatment with vehicle (0.5% carboxymethylcellulose, p.o.) or **isovaleramide** (500 mg/kg, p.o., 0.08 ml/gr of body weight) was initiated after a seven-day postoperative recovery period. After a 30 min. . . and a frequency greater than 1/sec. The results demonstrate the antiepiletogenic effect of a daily 500 mg/kg p.o. dose of **isovaleramide**, which delayed the increases in both seizure score and afterdischarge duration which normally develop during electrical kindling in the amygdala-kindled rat.

Although **isovaleramide** at this dose elicited a delay in the acquisition of seizure development, over time, the rats eventually developed full stage 5 seizures. We have shown in the Frings mouse that **isovaleramide** has a quick onset of action with a relatively short biological half-life. A greater antiepileptogenic effect may have occurred if. . .

CLM What is claimed is:

. . . wherein said compound is selected from the group consisting of 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-**isovaleramide**, 2-hydroxyisovaleramide, N-(2-acetamido)**isovaleramide**, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate, with the proviso that the treated pathology is not convulsions. . .

3. A method according to claim 1, wherein said pathology is **spasticity**.

6. A method according to claim 1, wherein said pathology is **headache**.

10. A method according to claim 1, wherein said compound is **isovaleramide**.

11. A method of providing neuroprotection to a patient suffering from a cerebral insult, comprising administering to said patient a. . . Y=--CO--, or --SO.sub.2--, and Z=H, CH.sub.2CO.sub.2H, or CH.sub.2CONH.sub.2 and wherein said compound is selected from the group consisting of 2-methyl **isovaleramide**, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-**isovaleramide**, 2-hydroxyisovaleramide, N-(2-acetamido) **isovaleramide**, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate.

12. A method according to claim 11, wherein said compound is **isovaleramide**.

13. A method of treating a pathology that is ameliorated by a modulation of CNS activity, comprising administering to a. . . or hops, wherein said extract comprises at least one compound that is hydrolyzed in vivo

to yield isovaleric acid or **isovaleramide**.

14. A method according to claim 13, wherein said pathology is **spasticity**.

15. A method according to claim 1, wherein said compound is 2-methyl **isovaleramide**.

25. A method according to claim 1, wherein said compound is 4-hydroxy-3-methyl-**isovaleramide**.

27. A method according to claim 1, wherein said compound is N-(2-acetamido)**isovaleramide**.

IT Anticonvulsants
IT Drug delivery systems
IT **Headache**
IT Nervous system depressants
IT Valerian (Valeriana)
(isovaleric acid and derivs. for treatment of spasticity and convulsions)
IT 503-74-2, Isovaleric acid 503-74-2D, Isovaleric acid, esters and amides
and salts **541-46-8**, Isovaleramide
(isovaleric acid and derivs. for treatment of spasticity and convulsions)

L10 ANSWER 3 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2004:83270 USPATFULL
TITLE: Methods and compounds for treating neurologic or neuropsychiatric disorders and identifying compounds to
treat the same
INVENTOR(S): Artman, Linda D, Salt Lake City, UT, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004063726	A1	20040401	
APPLICATION INFO.:	US 2003-467700	A1	20030809	(10)
	WO 2002-US3876		20020208	

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TRASK BRITT, P.O. BOX 2550, SALT LAKE CITY, UT, 84110
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
LINE COUNT: 1128
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . Isovaleric acid ("IVA") is an endogenous fatty acid resulting from the breakdown of leucine and fatty acids in the body. **Isovaleramide** ("IVM"), the amide of IVA is also an endogenous amide that has demonstrated anticonvulsant effects. IVA is a normal high. . .
SUMM . . . therapeutic action of fatty acid amides in a number of maladies, such as epilepsy, mood disorders, sleep disorders, restlessness syndromes, **migraine** headaches, movement disorders, **spasticity**, pain disorders, anxiety, and neurodegenerative disorders. There also exists a need in the art of increasing levels of endogenous and. . .

SUMM [0012] Yet another method of the invention relates to a method of treating epilepsy, a mood disorder, a **migraine headache**, a spastic condition, a restless limb syndrome, or a movement disorder by administering a FAAH inhibitor that inhibits the deamidation. . .

SUMM [0015] A particular embodiment of the invention relates to a method of identifying novel FAAHs by administering **isovaleramide** to a mammal and monitoring the activity of FAAHs and products resulting from the metabolism of the administered **isovaleramide**. Alternatively, FAAHs may be employed to screen for novel FAAH inhibitors or to develop novel FAAs that are more resistant. . .

SUMM . . . a disorder or disease of the nervous system including, but not limited to, epilepsy, pain, anxiety, sleep disorders, mood disorders, **migraine** headaches, spastic conditions, restless limb syndromes, movement disorders and neurodegenerative diseases. Also meant by "neurologic or neuropsychiatric disorder or disease". . .

SUMM . . . acid amides, and for which the method of the invention is particularly suited, include epilepsy, pain, sleep disorders, mood disorders, **migraine** headaches, spastic conditions, restless limb syndrome, anxiety, neurodegenerative diseases, and movement disorders. Administration of the FAAH inhibitors is equally effective. . .

SUMM . . . counterparts, arachidonate and oleic acid. These preferred FAAH inhibitors are particularly useful as agents for treatment of epilepsy, mood disorders, **migraine** headaches, spastic conditions, restless limb syndrome, or movement disorders. More specifically, FAAH inhibitors suitable for use with the present invention. . .

SUMM . . . or discovery of a mechanism of action of fatty acids, FAAs, or other pharmaceutical compounds (e.g., valproic acid, valpromide, or **isovaleramide**) which have been identified as active in the treatment of neurologic or neuropsychiatric disorders or diseases such as depression, pain, **spasticity**, migraines, mood disorders, and dysthymic disorders.

SUMM . . . models for Parkinson's disease. For multiple sclerosis, experimental autoimmune encephalomyelitis ("EAE") is a valid animal model. For the treatment of **migraine** headaches, the amygdala kindling model, retinal plasma extravasation model, or the inhibition neurogenic dural inflammation model may be appropriate animal. . .

SUMM [0046] A particular embodiment of the invention relates to a method of identifying novel FAAHs by administering **isovaleramide** to a mammal and monitoring the activity of FAAHs and products resulting from the metabolism of the administered **isovaleramide**. Alternatively, the method may be used to identify novel fatty acids, fatty acid amides, or fatty acid amide hydrolase inhibitors. The method comprises administering **isovaleramide** to a mammal and monitoring the activity of the fatty acid amide hydrolase and products resulting from the metabolism of the administered **isovaleramide**.

DETD Identifying an Inhibitor of Oleamide Hydrolase to Treat a **Migraine Headache**

DETD [0090] To identify an inhibitor of oleamide hydrolase that is useful in treating a **migraine headache**, the method described in Example 1 is followed, with the following changes. A known amount of a compound active as. . . inhibitor is tested in the neurogenic dural inflammation model, which is predictive of compounds that may be

effective therapies for **migraine** headaches. The compound is administered to a rat showing the symptoms of a **migraine headache**. The compound is administered to the rat based on its formulation. If the compound is formulated as a capsule or. . .

DETD [0091] The ability of the compound to treat the symptoms of the **migraine headache** (or inhibit neurogenic inflammation). in the rat is measured. If the compound is effective, the neurogenic inflammation is reduced or. . .

DETD . . . ability of the compound, in combination with the fatty acid amide or fatty acid, to treat the symptoms of the **migraine headache** (or inhibit neurogenic inflammation) is measured. If the neurogenic inflammation is reduced, the combination of the compound and fatty acid amide or fatty acid is identified as being useful to treat the **migraine headache**.

DETD Identifying an Inhibitor of Anandamide Amidase to Treat a **Migraine Headache**

DETD [0093] To identify an inhibitor of anandamide amidase that is useful in the treatment of a **migraine headache**, the method described in Example 21 is followed, except that anandamide amidase is used instead of oleamide hydrolase. As previously. . .

DETD Identifying a FAA or Fatty Acid to Treat a **Migraine Headache**

DETD [0094] To identify a novel FAA or fatty acid useful in the treatment of a **migraine headache**, the method of Example 3 is followed except that the known amount of fatty acid amide or fatty acid that. . . neurogenic dural inflammation model. The fatty acid amide or fatty acid is administered to a rat having symptoms of a **migraine headache**. The fatty acid amide or fatty acid is administered through an appropriate route based on its formulation. If the fatty. . .

DETD [0095] The ability of the administered fatty acid amide or fatty acid to treat the symptoms of the **migraine** (or inhibit neurogenic inflammation) is measured by observing the effects of the fatty acid amide or fatty acid on the. . .

DETD Identifying a FAA or Fatty Acid to Treat a **Migraine Headache**

DETD [0096] To identify a novel FAA or fatty acid useful in the treatment of a **migraine headache**, the method described in Example 23 is followed, except that anandamide amidase is used instead of oleamide hydrolase. The anandamide. . .

CLM What is claimed is:

. . . fatty acid amide, wherein said neurologic or neuropsychiatric disorder is selected from the group consisting of a mood disorder, a **migraine headache**, a spastic condition, a restless limb syndrome, a movement disorder, anxiety, epilepsy, or a neurodegenerative disease.

. . . or neuropsychiatric disorder is selected from the group consisting of epilepsy, pain, a sleep disorder, anxiety, a mood disorder, a **migraine headache**, a spastic neurodegenerative disease, and a movement disorder.

. . . or neuropsychiatric disorder is selected from the group consisting of epilepsy, pain, a sleep disorder, anxiety, a mood disorder, a **migraine headache**, a spastic condition, a restless

limb syndrome, a neurodegenerative disease, and a movement disorder.

IT **Headache**
(migraine; methods and compds. for the treatment of neurol. or neuropsychiatric disorders)

L10 ANSWER 4 OF 18 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004176768 EMBASE
TITLE: **Isovaleramide.**
AUTHOR: Mealy N.E.; Bayes M.
CORPORATE SOURCE: N.E. Mealy, Prous Science, P.O. Box 540, 08080 Barcelona, Spain
SOURCE: Drugs of the Future, (2004) 29/3 (293).
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 008 Neurology and Neurosurgery
032 Psychiatry
037 Drug Literature Index
LANGUAGE: English
TI **Isovaleramide.**
CT Medical Descriptors:
*epilepsy: DT, drug therapy
*bipolar disorder: DT, drug therapy
***migraine: DT, drug therapy**
neuromodulation
drug safety
drug tolerability
sustained release formulation
human
clinical trial
note
***isovaleramide: CT, clinical trial**
***isovaleramide: DT, drug therapy**
*nps 1776: CT, clinical trial
*nps 1776: DT, drug therapy
*valeramide: CT, clinical trial
*valeramide: DT, drug therapy
unclassified drug

L10 ANSWER 5 OF 18 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004330964 EMBASE
TITLE: New generation of valproic acid.
AUTHOR: Trojnar M.K.; Wierzchowska-Cioch E.; Krzyzanowski M.; Jargiello M.; Czuczwar S.J.
CORPORATE SOURCE: S.J. Czuczwar, Department of Pathophysiology, Skubiszewski Medical University, Jaczewskiego 8, PL 20-090 Lublin, Poland. czuczwarsj@yahoo.com
SOURCE: Polish Journal of Pharmacology, (2004) 56/3 (283-288).
Refs: 30
ISSN: 1230-6002 CODEN: PJPAE3
COUNTRY: Poland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index

038 Adverse Reactions Titles
050 Epilepsy
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
epilepsy: . . . SI, side effect
ECG abnormality: SI, side effect
drug cross reactivity
central nervous system disease: SI, side effect
digestive system function disorder: SI, side effect
headache: SI, side effect
dizziness: SI, side effect
nausea: SI, side effect
abdominal pain: SI, side effect
diarrhea: SI, side effect
sore throat: SI, side effect
dyspepsia:. . .
derivative: SC, subcutaneous drug administration
valproic acid: AE, adverse drug reaction
valproic acid: CM, drug comparison
valproic acid: DT, drug therapy
valproic acid: PD, pharmacology
3 methylbutanamide isovaleramide: AE, adverse drug reaction
3 methylbutanamide isovaleramide: CT, clinical trial
3 methylbutanamide isovaleramide: AN, drug analysis
3 methylbutanamide isovaleramide: CM, drug comparison
3 methylbutanamide isovaleramide: DV, drug development
3 methylbutanamide isovaleramide: DT, drug therapy
3 methylbutanamide isovaleramide: TO, drug toxicity
3 methylbutanamide isovaleramide: PK, pharmacokinetics
3 methylbutanamide isovaleramide: PD, pharmacology
3 methylbutanamide isovaleramide: PO, oral drug administration
valrocemide: AE, adverse drug reaction
valrocemide: CT, clinical trial
valrocemide: AN, drug analysis
valrocemide: CB, drug combination
valrocemide: CM,. . .

L10 ANSWER 6 OF 18 USPATFULL on STN DUPLICATE 1
ACCESSION NUMBER: 2003:184101 USPATFULL
TITLE: Treating a variety of pathological conditions, including **spasticity** and convulsions, by effecting a modulation of CNS activity with **isovaleramide**, isovaleric acid, or a related compound
INVENTOR(S): Artman, Linda D., Salt Lake City, UT, United States
Balandrin, Manuel, Sandy, UT, United States
Smith, Robert L., Lansdale, PA, United States
PATENT ASSIGNEE(S): NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6589994	B1	20030708
APPLICATION INFO.:	US 1999-258882		19990301 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 1997-US15272, filed

on 29 Aug 1997

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-25050P	19960830 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Rose, Shep K.	
LEGAL REPRESENTATIVE:	Foley & Lardner	
NUMBER OF CLAIMS:	1	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	7 Drawing Figure(s); 7 Drawing Page(s)	
LINE COUNT:	1745	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Treating a variety of pathological conditions, including **spasticity** and convulsions, by effecting a modulation of CNS activity with **isovaleramide**, isovaleric acid, or a related compound

AB Preparations and extracts of valerian, as well as **isovaleramide**, isovaleric acid, and certain structurally related compounds exhibit clinically significant pharmacological properties which implicate a treatment for a variety of pathological conditions, including **spasticity** and convulsions, which are ameliorated by effecting a modulation of CNS activity. The compositions in question generally are non-cytotoxic and. . .

SUMM The present invention provides methods of treating pathological conditions, such as **spasticity** and convulsions, the symptoms of which are alleviated by a modulation of activity in the central nervous system (CNS), without. . .

SUMM . . . disorders are characterized by a profound aberration in the normal function of the central nervous system (CNS). Such conditions include **spasticity**, strokes, spinal cord injuries, chronic neurodegenerative disorders and diseases such as Parkinson's and Huntington's diseases, Alzheimer's disease, and epilepsy. At. . .

SUMM Many agents currently employed in the treatment of pathologies such as **spasticity** and convulsions display troubling side-effect profiles which limit their long-term clinical utility. Among these agents, for example, are the benzodiazepines,. . . These side-effects severely limit the therapeutic potential for both drugs. It is apparent, therefore that improved and better-tolerated treatments for **spasticity**, convulsions, and other therapeutic indications are greatly to be desired.

SUMM . . . of the present invention to provide a method for alleviating one or more symptoms associated with a condition, such as **spasticity**, that is ameliorated by means of a centrally mediated decrease in muscle tone.

SUMM It is another object of the present invention to provide a novel prophylactic therapy for **migraine** and other **headache** pathologies.

SUMM . . . according to one aspect of the present invention, a method of using a compound selected from the group consisting of **isovaleramide**, a pharmaceutically acceptable ester of isovaleric acid, a pharmaceutically acceptable amide of isovaleric acid, and a compound selected from the group consisting of 2-methyl **isovaleramide**, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-

dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-**isovaleramide**, 2-hydroxyisovaleramide, N-(2-acetamido)**isovaleramide**, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate.

SUMM . . . to one embodiment of the invention, the pharmaceutically acceptable amide of isovaleric acid is selected from the group consisting of **isovaleramide**, N-ethyl **isovaleramide**, N-methyl **isovaleramide**, N,N-dimethyl **isovaleramide**, N-methyl,N-ethyl **isovaleramide**, N-(2-acetamido) **isovaleramide** ("N-isovaleryl glycinamide"), and N-isovaleryl GABA.

SUMM . . . another embodiment of the invention, the treated pathology is an affective mood disorder, convulsions, a central neuropathic pain syndrome, a **headache**, or a restessness syndrome. In still another embodiment, the pathology is **spasticity** that is ameliorated by a centrally mediated decrease in muscle tone. In a further embodiment, the treated pathology is, a. . .

SUMM . . . provided for an extract of Valerianaceae, cramp bark, black haw, or hops in a method of treating a symptom of **spasticity**, where the extract comprises at least one compound that is hydrolyzed in vivo to yield isovaleric acid or **isovaleramide**. By the same token, the present invention provides a method for alleviating a symptom of **spasticity** in a subject in need of such treatment, comprising the step of administering a therapeutically effective amount of an extract. . .

DRWD FIGS. 1a and 1b depicts the structures of compounds, including **isovaleramide**, capable of inducing a modulation of the central nervous system.

DRWD FIG. 2 portrays the effect of **isovaleramide** (at 300 mg/kg, i.p.) on gross observational **spasticity** scores elicited by a metal probe applied to the abdomen in the chronic spinalized rat. Each rat served as its. . .

DRWD FIG. 3 illustrates a time-dependent reduction of the flexor reflex, an electrophysiological measure of **spasticity**, in the chronic spinalized rat. The effects of **isovaleramide** (300 mg/kg p.o.), baclofen (10 mg/kg s.c.), and vehicle (water, 12 ml/kg p.o.) are shown at pre-treatment (time zero) and at 30, 60, 90, and 120 minutes post-administration. **Isovaleramide** caused a significant decrease in the magnitude of the flexor reflex, comparable to that observed with baclofen.

DRWD FIG. 4 shows a dose-response relationship for **isovaleramide** and baclofen, a known antispasticity agent. **Isovaleramide** and baclofen produced a similar dose-dependent reduction of the flexor reflex in the chronic spinalized rat. The responses from FIG.. . .

DRWD FIG. 5 shows that **isovaleramide** was effective in reducing in a dose-dependent manner the generalized seizure responses of fully kindled rats. **Isovaleramide** decreased the mean seizure score and the afterdischarge duration in amygdala-kindled rats, showing that it exerts anticonvulsant activity against both. . .

DRWD FIG. 6 illustrates the antiepileptogenesis effect of a daily 500 mg/kg p.o. dose of **isovaleramide** compared to controls. **Isovaleramide** elicited a delay in the rate of increase in both seizure score and afterdischarge duration (not shown) which normally

develop. . .

DETD Isovaleric acid and its pharmaceutically acceptable salts, amides such as **isovaleramide**, and alcohol esters such as ethyl isovalerate and glyceryl triisovalerate can be administered in vivo to effect a modulation of. . . or no accompanying paralysis), eliciting a calmative effect (with little or no sedation), or ameliorating an ambulatory syndrome such as **spasticity** (with little or no accompanying weakness or flaccidity).

DETD A number of pathologies, exemplified by affective mood disorders (i.e. bipolar disorder), headaches (chronic, cluster, **migraine**), restlessness syndromes, neuropathic pain, movement disorders, **spasticity**, convulsions, cerebral insult, neurodegeneration, and substance abuse have at least one symptom that is usefully alleviated by

effecting a modulation. . . pathology may be treated with a therapy where, pursuant to the present invention, that individual receives a pharmaceutical formulation of **isovaleramide**, isovaleric acid, or a related compound.

DETD SPASTICITIY: **Spasticity** may be "defined as an upper [i.e., CNS] motor neuron disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon

jerks resulting from hyperexcitability of the stretch reflex." Lance, Symposia synopsis in **SPASTICITY**-DISORDERED MOTOR CONTROL, Feldman et al. (eds.) (1980) (Symposia Specialists, distributed by Year Book Medical Publishers). An increase in tonic stretch. . .

DETD Major disease states and conditions associated with **spasticity** include multiple sclerosis, cerebral palsy, stroke, trauma or injury to the spinal cord, and closed head trauma. There are "positive symptoms" that can occur with **spasticity**, such as the Babinski response, painful flexor or extensor spasms, increased or exaggerated deep tendon reflexes, and clonus. Other symptoms,. . . paresis" (spastic paralysis). Pain, impairment of sleep, and various degrees of loss of general motor function are also associated with **spasticity**.

DETD The pathological states observed in **spasticity** are fundamentally different at the physiological level from the commonly experienced acute muscular aches, strains, and sprains that occur from. . . or localized symptoms are commonly treated with so-called "antispasmodic" or "spasmolytic" agents. Such agents generally are not useful in treating **spasticity**. Cedarbaum & Schleifer, "Drugs for Parkinson's Disease, **Spasticity** and Acute Muscle Spasms," in GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 8th ed. [hereafter GOODMAN'S AND GILMAN'S], pages. . .

DETD . . . decrease in muscle tone and, hence, are useful for the acute or

chronic alleviation of one or more symptoms of **spasticity**. In the context of the present invention, "**spasticity**" refers to a heightened tone of skeletal muscle which is manifested by symptoms exemplified by but not limited to painful. . . jerks, and clonus. The

phrase "antispasticity agent" refers here to a composition that is useful for the symptomatic treatment of **spasticity**, as demonstrated by the alleviation of at least one of the following manifestations of **spasticity**: painful flexor or extensor spasms, increased or exaggerated deep tendon reflexes, hyperreflexia, loss of dexterity, muscular weakness, exaggerated tendon jerks, and clonus. Accordingly, the "alleviation" of **spasticity** refers here to the lessening of one or more symptoms of **spasticity**,

including, but not limited to, painful flexor or extensor spasms, increased or exaggerated deep tendon reflexes, hyperreflexia, loss of dexterity,. . .

DETD **Spasticity** is associated with multiple sclerosis, stroke, head trauma, spinal cord injuries, cerebral palsy, and other neurodegenerative diseases, disorders, and conditions. **Spasticity** is distinct from acute muscle spasms, which may be associated with a variety of conditions different from those leading to **spasticity**. These acute muscle spasm-causing conditions include trauma, inflammation, anxiety, and/or pain.

DETD The difference between **spasticity** and acute muscle spasms is illustrated by the fact that agents useful for the treatment of muscle spasms are not useful for treating **spasticity** associated with chronic neurological diseases. Cedarbaum & Schleifer (1990), supra. Likewise, agents used heretofore to treat **spasticity** associated with chronic neurological disorders have not been employed in treating acute muscle spasms, except for the benzodiazepines, such as. . . contrast, the present invention achieves a centrally mediated decrease in muscle tone which, in turn, addresses the particular symptoms of **spasticity**.

DETD HEADACHES: Headaches of the **migraine** type (Hering & Kuritzky, Cephalalgia 12: 81-84 (1992)), the cluster type (Hering & Kuritzky, loc. cit. 9: 195-98 (1989)) and the chronic type (Mathew & Sabiha, **Headache** 31: 71-74 (1991)) have been treated by the administration of valproate and other anticonvulsants. The compositions of the present invention also will alleviate symptoms associated with each of the three **headache** types, without the adverse side effects of valproate and other anticonvulsant therapy.

DETD . . . aqueous or hydroalcoholic extracts or tinctures, has been determined to be the ester hydrolysis product, isovaleric acid. Ammonium isovalerate and **isovaleramide** are produced in ammoniated tinctures. Balandrin et al., J. Toxicol.-Toxin Rev. 14: 165 (1995). The structures of **isovaleramide** and related compounds are depicted in FIG. 1. In this way, the chemically labile valepotriates and other valerian-derived monoterpenoid-isovalerate esters,. . .

DETD **Isovaleramide** has been isolated from valerian plants, most probably as an isolation artifact following treatment with ammonia. Buckova et al., Cesk.. . . 88: 86063z (1978); see also Bos et al. and Fuzzati et al., Phytochem. Anal. 7: 143, 76 (1996). More recently, **isovaleramide** was shown to exhibit low acute toxicity in vivo, no mutagenic potential, and clinically useful anxiolytic properties (U.S. Pat. No. 5,506,268; PCT application WO 94/28,888). Methods for preparing **isovaleramide** are well known.

DETD Extracts of medicinal plants that are useful for treating the symptoms of **spasticity** can be prepared by aqueous, hydroalcoholic, or alcoholic extraction, or by extraction with other suitable solvents using methods well known. . . the present invention, useful extracts contain at least one of the following: isovaleric acid, its salts or complexes, ethyl isovalerate, **isovaleramide**, N-ethyl **isovaleramide**, and their chemical precursors. Useful extracts also share the common property of releasing isovaleric acid and/or **isovaleramide** upon hydrolysis in vivo. Standard methods for preparing such extracts can be found in pre-1950 editions of the U.S. PHARMACOPOEIA. . .

DETD In addition to **isovaleramide**, various N-substituted amides of isovaleric acid may be used in the inventive methods. These amides can be prepared by methods. . . example, March, ADVANCED ORGANIC CHEMISTRY: REACTIONS, MECHANISMS, AND STRUCTURE, 4th ed. (John Wiley and Sons 1992). Preferred amides include N-ethyl **isovaleramide**, N-methyl **isovaleramide**, N,N-dimethyl **isovaleramide**, N-methyl, N-ethyl isovaleramnide, N-(2-acetamido)**isovaleramide** ("N-isovaleryl glycinamide"), and N-isovaleryl GABA. See, for exarnple, Tanaka et al., J. Biol. Chem. 242: 2966 (1967).

DETD . . . present invention also is directed to compounds and methods of using compounds that, by virtue of their structural similarity to **isovaleramide**, share similar pharmacological activities. These compounds generally share the common structure: ##STR1##

DETD . . . FIGS. 1a and 1b and include substituted isovaleramides such as 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-**isovaleramide**, 2-hydroxyisovaleramide, and 2,2-dimethyl-n-butyramide. For each of these compounds that contains one or more asymmetric centers, the present invention specifically includes.

. .

DETD N,N-Diethyl **isovaleramide** ("Valyl"), although purported to possess CNS depressant (sedative) activity, recently has been shown to possess CNS stimulant (convulsant) properties; see. . . of the isovalerate esters, these substituted amides should be hydrolyzed in vivo (in this case, via hepatic amidase enzymes), releasing **isovaleramide** or isovaleric acid.

DETD . . . present invention also is directed to certain sulfonamide, sulfamate, and carbamate compounds that, by virtue of their structural similarity to **isovaleramide**, share similar pharmacological activities. Preferred sulfonamides and sulfamates include 2-methyl-1-propylsulfonamide, 1-methylethyl sulfamate, and 2-methyl-1-propyl sulfamate. Preferred carbamates include isobutylcarbamate (CH.sub.3).sub.2CHCH.sub.2OCONH.sub.2). . .

DETD Certain of the compounds and preparations discussed above represent alternative forms for delivering isovaleric acid or **isovaleramide** in vivo. In cases such as isovaleryl salicylate and ethyl isovalerate, the pharmacologically active moiety corresponding to the alcohol portion. . . expected to exhibit a "Tylenol.RTM.-like" effect, similar to acetaminophen as well as the effect expected from the isovaleric acid or **isovaleramide** moiety. Such novel chemical combinations of a previously known, pharmacologically active alcohol, phenol, or primary or secondary amine with isovaleric. . .

DETD . . . example, in Green, "Protective Groups in Organic Synthesis", Wiley (1981), prior to preparation of the acid chloride. 2-hydroxy and 3-hydroxy **isovaleramide** are metabolites of **isovaleramide** in vivo, and can be isolated in high yield from the urine of a patient being treated with **isovaleramide**.

DETD . . . agent is physiologically significant if the presence of the agent results in the alleviation of one or more symptoms of

spasticity, while an anticonvulsant agent is physiologically significant if the presence of the agent results in the reduction of the severity,. . .

DETD **Isovaleramide** and related compounds can be administered orally using solid oral dosage forms such as enteric-coated tablets, caplets, gelcaps, or capsules, or via liquid oral dosage forms such as syrups or elixirs. The indicated dosage of **isovaleramide** and related compounds as antispasticity agents is on the order of 50-1200 mg per dose or 1-20 mg/kg body weight.. . . in the form of drops (with a dropper from a "concentrate" preparation) for oral administration. In addition, compounds such as **isovaleramide** may be formulated into chewing gum to facilitate oral delivery and absorption.

DETD Alternatively, **isovaleramide** and related compounds can be administered by injection or other systemic routes, such as IV, transdermal or transmucosal administration, for. . .

DETD In addition to a use in humans, **isovaleramide** and related compounds can be used, for example, as antispasticity agents or anticonvulsant agents, in animals such as cats, dogs,. . . administration via suppositories), or orally by addition to food or drink. As an antispasticity agent, the indicated oral dosage of **isovaleramide** and/or related compounds per kilogram of body weight of such animals is about 50-1200 mg/kg, depending upon the species of. . .

DETD The indicated oral dosage of **isovaleramide** and/or related compounds per kilogram body weight as anticonvulsant agents for animals is in the range of about 50-1200 mg/kg,. . .

DETD The present invention thus contemplates a variety of pharmaceutical compositions containing the active compounds described above (including **isovaleramide**, isovaleric acid, and/or its pharmaceutically acceptable salts, substituted amides, alcohol esters, sulfonamide, sulfamate, and carbamate analogs) as active ingredients that. . . pharmaceutical formulations which are outside the scope of the present invention, the common feature of the present formulations is that **isovaleramide**, isovaleric acid, and/or its pharmaceutically acceptable salts, substituted amides, alcohol esters, and sulfonate, sulfamate, and carbamate analogs, are present in. . .

DETD It is further understood that **isovaleramide** and/or related compounds can be used in combination with other pharmaceutically active ingredients.

DETD The mutant spastic mouse is a homozygous mouse that carries an autosomal recessive trait of genetic **spasticity**. The mouse is normal at birth, and then the mouse develops a coarse tremor, abnormal gait, skeletal muscle rigidity, and. . . Is synthesis of GABA, such as valproate and the benzodiazepines, are effective compounds to ameliorate some of the symptoms of **spasticity** in this model, as well as in humans.

DETD The assessment of **spasticity** in the mutant spastic mouse can be performed by electrophysiological assessment similar to the EMG recordings described below. One can. . .

DETD There are several models of **spasticity** including the acute decerebrate rat, the acute or chronic spinally transected rat, and the chronically spinal cord-lesioned rat. (Wright, J.,. . . Clin Orthop 253:12, 1990). The acute models, although of proven value in elucidating the mechanisms involved in the development of **spasticity**, have

come under criticism due to the fact that they are acute. The animals usually die or have total recovery from **spasticity**. The **spasticity** develops immediately upon intervention, unlike the **spasticity** that evolves in the human condition of **spasticity**, which most often initially manifests itself as a flaccid paralysis. Only after weeks and months does **spasticity** develop in humans. Some of the more chronic-lesioned or spinally transected models of **spasticity** do post-operatively show flaccid paralysis. At approximately four weeks post-lesion/transection, the flaccidity changes to **spasticity** of variable severity. Although all of these models have their own particular disadvantages and lack of true representation of the human spastic condition, they have provided much information about the nature of **spasticity**. These models have also provided methods to test various treatment paradigms that have led to similar treatments being tested in. . .

DETD Neurogenic inflammation within the meninges has been proposed as an event in the underlying pathology of **migraine** headaches. Lee et al., Brit. J. Pharmacol. 116: 1661-67 (1995). Compounds are tested for their ability to block the leakage. . .

DETD The therapeutic effects of **isovaleramide**, isovaleric acid, and related compounds in various of the assays described above, combined with a general lack of toxicity, make the compounds of the present invention ideal agents for the treatment of the pathologies described above, including **spasticity** and convulsions/seizures. With this background, the present invention will be understood more readily by reference to the following examples, which. . .

DETD Use of a Valetian Preparation to Alleviate Symptoms of **Spasticity** Associated with Multiple Sclerosis

DETD Use of a Valerian Preparation to Alleviate Symptoms of **Spasticity** Associated with Spinal Cord Injury

DETD A human male subject, age 38, suffers symptoms of **spasticity** (hyperreflexia, tendon jerks, and extensor spasms) that evolved from an earlier injury to the spinal cord. All of these symptoms. . .

DETD **Isovaleramide** Antispasticity Tests

DETD (1) Assessment of **Spasticity** in Chronic Spinally Transected Rats

DETD . . . all animals regained bladder control and were no longer given antibiotic treatment. Advokat, Brain Res. 684: 8 (1995). Assessment of **spasticity** was performed before and after drug treatment such that each animal served as its own control.

DETD Initial assessment of **spasticity** was performed by the subjective scoring method of rating the resulting **spasticity** response elicited with an innocuous stimulus, i.e., a metal probe, that was pressed against the lower abdomen at four specific. . . zero (no spastic response in all four trials) to four (a maximum, tonic-clonic reaction elicited in all four trials). All **spasticity** scores, pre- and post-treatment, were transformed to indicate the percent **spasticity** such that a score of {fraction (0/4)}=0%, 1/4=25%, etc. These raw or normalized scores were analyzed with a one-way repeated. . .

DETD As shown in FIG. 2, **isovaleramide** at a dose of 300 mg/kg, i.p., was efficacious at 15, 30, 60, and 120 minutes post-administration in reducing the **spasticity** scores (45-65%). By the next day, i.e., by 1440 minutes (24 hours), the **spasticity** scores had essentially returned to baseline values. No overt behavioral toxicity or

motor impairment was observed at this dose. The. . .

DETD . . . the flexor-reflex response (FIG. 3) before treatment and at each of 30, 60, 90, and 120 minutes following administration of **isovaleramide** (300 mg/kg p.o.), baclofen (10 mg/kg s.c.) and vehicle (water, 12 ml/kg p.o.), respectively.

DETD **Isovaleramide** was shown to reduce the magnitude of the flexor-reflex responses, at all time points in a chronic spinalized rat with. . .

DETD In FIG. 4, the responses from FIG. 3 and additional doses of **isovaleramide** and baclofen are converted to a total-area-under-the-curve format, covering the entire, two-hour measurement period. All drug-treated groups differed significantly from.

. .

DETD Administered i.p. in the rat, **isovaleramide** induced no changes from saline-injected controls at doses up to 256 mg/kg. At 512 mg/kg, slight sedation from 60 to. . .

DETD **Isovaleramide**, administered at doses of 128, 256, and 512 mg/kg (i.p.) 60 minutes before a test on the rotarod, did not. . .

DETD

TABLE 1

Effects of **Isovaleramide** and Diazepam in the Rotarod Test in the Rat

Number.sup.b Drop-Off Time (sec)

of Rats Mean .+-. % change from

Dose of: Falling S.E.M. t value control

Isovaleramide

(mg/kg).sup.a

0 5 135.5 .+-. -- --

18.0

128 6 134.5 .+-. 0.036 -1%

20.7

256 7 98.4 .+-. 1.261 -27%

23.3.sup.c

512. . .

DETD **Isovaleramide**, administered at doses up to 512 mg/kg (i.p.) 15 minutes before a test on the rotarod in the Frings mouse,. . .

DETD The results of Table 2 demonstrate the anticonvulsant activity of **isovaleramide** when administered i.p. in this animal model of epilepsy. Isovaleramnide also displayed a quick onset and a relatively short duration. . . was observed at this time point. At doses markedly higher than those providing anticonvulsant activity (>300 mg/kg), animals treated with **isovaleramide** displayed behavioral toxicity that was characterized by their inability to maintain their balance on the rotarod. No notable toxicity was. . .

DETD Therefore, despite the relatively low potency of **isovaleramide** in this model, it still displayed a relatively good separation between activity and toxicity. **Isovaleramide** thus had a surprising and unexpected efficacy, based on existing structure-activity relationships for amides and their corresponding acids, as an anticonvulsant in the Frings audiogenic seizure-susceptible mouse model of reflex epilepsy. The activity profile of **isovaleramide** is similar to that of the broad-spectrum anticonvulsant, sodium valproate. Compounds similar in structure to valproate as well as isovaleric. . .

DETD

TABLE 2

Effect of **Isovaleramide** on the Audiogenic Seizure Susceptibility of Frings Mice Following Intraperitoneal Administration

Dose of **Isovaleramide** (mg/kg, i.p.)	Number.sup.a Seizure Protected Score .+-. S.E.M.	Number.sup.a Showing Toxicity of Eight Tested
75	4.4 .+-. 0.6	1 of Eight Mice Tested
112.5	4.0 .+-.. . .	

DETD The results of Table 3 demonstrate that **isovaleramide** displayed anticonvulsant activity when administered orally in this aniimal model of epilepsy.

DETD

TABLE 3

Effect of **Isovaleramide** on the Audiogenic Seizure Susceptibility of Frings Mice Following Oral Administration

Dose of	Number.sup.c Number.sup.a Showing Protected	Number.sup.a Showing Toxicity ED.sub.50 of. . .

DETD The results of Table 4 and Table 5 demonstrate that the **isovaleramide** analogs N-(2-acetamido)**isovaleramide** and 2-methylisovaleramide displayed anticonvulsant activity when administered orally in this animal model of epilepsy.

DETD

TABLE 4

Effect of N-(2-acetamido) **isovaleramide** on the Audiogenic Seizure Susceptibility of Frings Mice Following Oral Administration

Dose of N-(2-acetamido)	Number.sup.a Protected	Number.sup.a Showing Protected	Showing Toxicity. . .

DETD . . . the structure-activity relationships of anticonvulsant activity around compounds similar to valproate have taught away from simple, unsubstituted compounds such as **isovaleramide**. It is thus a surprising and unexpected observation that **isovaleramide** has demonstrated an efficacy profile similar to that of valproate in the Frings audiogenic seizure-susceptible mouse model and a similar separation of activity between efficacy and toxicity as measured by rotarod performance. These observations indicate that **isovaleramide** is an effective therapeutic agent as a broad-spectrum anticonvulsant. **Isovaleramide** is known for its relative lack of toxicity in mutagenicity and cytotoxicity tests. See U.S. Pat. No. 5,506,268 and PCT. . .

DETD **Isovaleramide** was evaluated for its, ability to block the expression of amygdala-kindled seizures in fully kindled rats. **Isovaleramide** was evaluated for its ability to block the kindled motor seizure (seizure scores of 4 and 5) and limbic behavioral. . .

DETD . . . ms biphasic 150 uA pulses that were delivered once daily until 10 consecutive stage 5 seizures were evoked. Testing of **isovaleramide** was initiated after a one-week, stimulus-free period. On the compound test day, rats displaying a stage 5 seizure were divided into multiple treatment groups (i.e. vehicle control and

isovaleramide treatment). Sixty minutes after oral dosing, individual rats received a 300 uA, 1 sec duration stimulation and their seizure score. . .

DETD **Isovaleramide** was effective in reducing in a dose-dependent manner the generalized seizure responses of fully kindled rats. **Isovaleramide** decreased the mean seizure score and the afterdischarge duration showing that it exerts anticonvulsant activity against both focal(seizure score 1-3). . .

DETD . . . following coordinates with Bregrna as zero: AP-2.2 mm, ML-4.7 mm, DV-8.7 mm. Chronic treatment with vehicle (0.5% carboxymethylcellulose, p.o.) or **isovaleramide** (500 mg/kg, p.o., 0.08 ml/gr of body weight) was initiated after a seven-day postoperative recovery period. After a 30 min. . . and a frequency greater than 1/sec. The results demonstrate the antiepiletogenic effect of a daily 500 mg/kg p.o. dose of **isovaleramide**, which delayed the increases in both seizure score and afterdischarge duration which normally develop during electrical kindling in the amygdala-kindled rat.

Although **isovaleramide** at this dose elicited a delay in the acquisition of seizure development, over time, the rats eventually developed full stage 5 seizures. We have shown in the Frings mouse that **isovaleramide** has a quick onset of action with a relatively short biological half-life. A greater antiepileptogenic effect may have occurred if. . .

CLM What is claimed is:

1. A method for treating convulsions, comprising administering an effective amount of **isovaleramide** to a subject suffering from epilepsy and at risk of suffering convulsions.

IT Anticonvulsants
IT **Convulsion**
IT Epilepsy
IT Human
IT Nervous system agents
IT Valeriana
(convulsions treatment with isovaleramide)
IT **541-46-8**, Isovaleramide 66309-91-9 241816-75-1
(convulsions treatment with isovaleramide)

L10 ANSWER 7 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2003:71939 USPATFULL
TITLE: Dopamine analog amide
INVENTOR(S): Shashoua, Victor E., Belmont, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003050226	A1	20030313
APPLICATION INFO.:	US 2002-173970	A1	20020618 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-901209, filed on 9 Jul 2001, GRANTED, Pat. No. US 6407137 Continuation of Ser. No. US 1999-450310, filed on 29 Nov 1999, GRANTED, Pat. No. US 6258836 Continuation-in-part of Ser. No. US 1995-462820, filed on 5 Jun 1995, GRANTED, Pat. No. US 5994392 Continuation of Ser. No. US 1993-80675, filed on 21 Jun 1993, ABANDONED Continuation of Ser. No. US

1992-952191, filed on 28 Sep 1992, ABANDONED Continuation of Ser. No. US 1990-577329, filed on 4 Sep 1990, ABANDONED Continuation-in-part of Ser. No. US 1990-535812, filed on 11 Jun 1990, ABANDONED Continuation of Ser. No. US 1989-315134, filed on 24 Feb 1989, GRANTED, Pat. No. US 4933324 Continuation-in-part of Ser. No. US 1988-160667, filed on 26 Feb 1988, GRANTED, Pat. No. US 4939174

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Edward R. Gates, Esq., Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1313
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . muscle relaxants, anti-parkinson agents, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents, local anesthetics, anti-spasmodics and muscle contractants, prostaglandins, anti-bacterials, anti-septics, anti-depressants, anti-**migraine** preparations, central nervous system stimulants, imaging agents, specific targeting agents, proteins, peptides, anti-viral agents, anti-psychotic agents, anti-addiction agents and anti-emetics.

DETD . . . which produce a hypnotic effect. Hypnotics include pentobarbital sodium, phenobarbital, secobarbital, thiopental and mixtures, thereof, heterocyclic hypnotics, dioxopiperidines, glutarimides, diethyl **isovaleramide**, .alpha.-bromoisovaleryl urea, urethanes and disulfanes.

DETD [0118] Anti-**migraine** preparations are substances capable of preventing or relieving **migraine** headaches. Examples of such substances include ergotamine tartrate, caffeine, dihydroengotamine mesylate propanolol HCl, acetominophin, and salicylic acid.

CLM What is claimed:

. . . anti-convulsant, muscle relaxant, anti-hypertensive agent, analgesic, anti-pyretic agent, anti-inflammatory agent, local anesthetic, muscle contractant, prostaglandin, anti-bacterial agent, anti-septic agent, anti-depressant, anti-**migraine** preparation, imaging agent, specific targeting agent, protein, peptide, anti-viral agent, anti-psychotic agent, anti-addiction agent, or anti-emetic agent.

L10 ANSWER 8 OF 18 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003319044 EMBASE
TITLE: Current and future aspects of the drug therapy of epilepsy.
AUTHOR: Tugwell C.
SOURCE: Hospital Pharmacist, (2003) 10/7 (296-302).
Refs: 11
ISSN: 1352-7967 CODEN: HSPMFF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index

038 Adverse Reactions Titles
050 Epilepsy
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*epilepsy: DT, drug therapy
*anticonvulsant therapy
seizure: DT, drug therapy
pregnancy
breast feeding
clinical pharmacy
pharmacist
patient counseling
drug choice
drug efficacy
drug safety
side effect: SI, side effect
drowsiness: SI, side effect
headache: SI, side effect
fatigue: SI, side effect
vertigo: SI, side effect
nausea: SI, side effect
visual field defect: SI, side effect
rash: SI, side effect
Stevens. . .
agent: IT, drug interaction
*anticonvulsive agent: DT, drug therapy
*anticonvulsive agent: PK, pharmacokinetics
*anticonvulsive agent: PD, pharmacology
*refinamide: DV, drug development
*valproyl glycinamide: DV, drug development
***isovaleramide: DV, drug development**
*sdp 421: DV, drug development
vigabatrin: AE, adverse drug reaction
vigabatrin: DT, drug therapy
lamotrigine: AE, adverse drug reaction
lamotrigine: CR, drug. . .

L10 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:690451 CAPLUS
DOCUMENT NUMBER: 140:245670
TITLE: New CNS-active drugs which are second-generation valproic acid: can they lead to the development of a magic bullet?
AUTHOR(S): Isoherranen, Nina; Yagen, Boris; Bialer, Meir
CORPORATE SOURCE: Department of Pharmaceutics, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel
SOURCE: Current Opinion in Neurology (2003), 16(2), 203-211
CODEN: CONEEX; ISSN: 1350-7540
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT
AB A review. Valproic acid (VPA) is one of the four first line antiepileptic

drugs (AEDs). VPA is also an effective drug in **migraine** prophylaxis and in treatment of bipolar disorders. The use of VPA is limited by its two rare but potentially life-threatening side effects, teratogenicity and hepatotoxicity, and it is the least potent of the established AEDs. Consequently, there is an incentive to develop a second-generation VPA. A successful, second-generation VPA would need to possess the following characteristics: broad-spectrum antiepileptic activity; better potency than VPA; and lack of teratogenicity and hepatotoxicity. These characteristics would give such a drug the potential to be utilized in epilepsy and other CNS disorders. Intensive research has been carried out in order to develop a second-generation VPA that would be more potent and safer than VPA. Amide derivs. of VPA have shown particular value as potential follow-up compds. and have better in-vivo performance than VPA. Several CNS-active valproylamides are more potent as antiepileptics than VPA, they possess broad-spectrum antiepileptic activity, and have been found to be non-teratogenic in animal models. The amide analogs of VPA that emerged from structure-pharmacokinetic-pharmacodynamic relationship studies as promising second-generation compds. are: N-methyl-tetramethylcyclopropane carboxamide, (2S,3S)-valnoctamide, (R)-propylisopropyl acetamide and valproyl glycinamide. At present there are three compds. in clin. trials in patients with epilepsy that can be regarded as second-generation VPA: valproyl glycinamide, 3-methylbutanamide or **isovaleramide**, and SPD421 (DP-VPA). For any one of these second-generation valproic acids to become a successful follow-up compd. to VPA, it has to fulfil the above criteria and also possess favorable pharmacokinetics.

IT **Headache**
(**migraine**; new CNS-active drugs which are second-generation valproic acids)

IT **541-46-8**, 3-Methylbutanamide 92262-58-3 171722-69-3 189189-75-1 247182-95-2 669771-20-4
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new CNS-active drugs which are second-generation valproic acids)

L10 ANSWER 10 OF 18 USPATFULL on STN

ACCESSION NUMBER:	2002:242829 USPATFULL
TITLE:	Divalproex sodium dosage forms and a process for their production
INVENTOR(S):	Qui, Yihong, Gurnee, IL, UNITED STATES Chermak, Todd E., Grayslake, IL, UNITED STATES Engh, Kevin R., Kenosha, WI, UNITED STATES Faitsch, Lynn, Libertyville, IL, UNITED STATES Slade, Russell T., Lindenhurst, IL, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002132010	A1	20020919	
APPLICATION INFO.:	US 2000-747912	A1	20001222	(9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	ROSS PRODUCTS DIVISION OF ABBOTT LABORATORIES, DEPARTMENT 108140-DS/1, 625 CLEVELAND AVENUE, COLUMBUS, OH, 43215-1724
NUMBER OF CLAIMS:	19
EXEMPLARY CLAIM:	1

NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 1080
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD [0023] Divalproex sodium is effective as an antiepileptic agent, in the treatment of **migraine** and for bipolar disorders. Methods for its preparation may be found in U.S. Pat. Nos. 4,988,731 and 5,212,326, the contents. . .
DETD . . . in which one of the propyl chains have been eliminated from the
molecule. One of these entities is known as **isovaleramide**. It's structure and activity are described in U.S. Pat. Nos. 5,763,494 and 5,506,268, the contents of both which are hereby. . .
DETD [0036] **Isovaleramide** may be represented by the structure above in which Z is H, Y is CO, X is CH.sub.2 and both. . .

L10 ANSWER 11 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2002:235094 USPATFULL
TITLE: Solid dosage forms of divalproex sodium
INVENTOR(S): Qiu, Yihong, Gurnee, IL, UNITED STATES
Engh, Kevin R., Kenosha, WI, UNITED STATES
Faitsch, Lynn, Libertyville, IL, UNITED STATES
Slade, Russell T., Lindenhurst, IL, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002127277	A1	20020912	
APPLICATION INFO.:	US 2000-748659	A1	20001222	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ROSS PRODUCTS DIVISION OF ABBOTT LABORATORIES, DEPARTMENT 108140-DS/1, 625 CLEVELAND AVENUE, COLUMBUS,
OH, 43215-1724
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 851
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . as a medication. It and other valproate compounds have been used in the treatment of neurological conditions such as epilepsy, **migraine**, and mania. As its name implies, valproic acid contains a carboxylic acid function. This makes its salt extremely hydrophilic (i.e.. . .
SUMM [0023] Divalproex sodium is effective as an antiepileptic agent, in the treatment of **migraine** and for bipolar disorders. Methods for its preparation may be found in U.S. Pat. Nos. 4,988,731 and 5,212,326, the contents. . .
SUMM . . . in which one of the propyl chains have been eliminated from the
molecule. One of these entities is known as **isovaleramide**. It's structure and activity are described in U.S. Pat. Nos. 5,763,494 and 5,506,268, the contents of both which are hereby. . .
SUMM [0036] **Isovaleramide** may be represented by the structure above in which Z is H, Y is CO, X is CH.sub.2 and both. . .

L10 ANSWER 12 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2001:237996 USPATFULL
TITLE: Dopamine analog amide
INVENTOR(S): Shashoua, Victor, Belmont, MA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001056116	A1	20011227
	US 6407137	B2	20020618
APPLICATION INFO.:	US 2001-901209	A1	20010709 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-450310, filed on 29 Nov 1999, UNKNOWN
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Edward R. Gates, Esq., Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1314
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . muscle relaxants, anti-parkinson agents, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents, local anesthetics, anti-spasmodics and muscle contractants, prostaglandins, anti-bacterials, anti-septics, anti-depressants, anti-**migraine** preparations, central nervous system stimulants, imaging agents, specific targeting agents, proteins, peptides, anti-viral agents, anti-psychotic agents, anti-addiction agents and anti-emetics.

DETD . . . which produce a hypnotic effect. Hypnotics include pentobarbital sodium, phenobarbital, secobarbital, thiopental and mixtures, thereof, heterocyclic hypnotics, dioxopiperidines, glutarimides, diethyl **isovaleramide**, .alpha.-bromoisovaleryl urea, urethanes and disulfanes.

DETD [0118] Anti-**migraine** preparations are substances capable of preventing or relieving **migraine** headaches. Examples of such substances include ergotamine tartrate, caffeine, dihydroengotamine mesylate propanolol HCl, acetominophin, and salicylic acid.

CLM What is claimed:
. . . anti-convulsant, muscle relaxant, anti-hypertensive agent, analgesic, anti-pyretic agent, anti-inflammatory agent, local anesthetic, muscle contractant, prostaglandin, anti-bacterial agent, anti-septic agent, anti-depressant, anti-**migraine** preparation, imaging agent, specific targeting agent, protein, peptide, anti-viral agent, anti-psychotic agent, anti-addiction agent, or anti-emetic agent.

L10 ANSWER 13 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2001:107918 USPATFULL
TITLE: Dopamine analog amide
INVENTOR(S): Shashoua, Victor E., Brookline, MA, United States
PATENT ASSIGNEE(S): Protarga, Inc., Conshohocken, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6258836	B1	20010710
APPLICATION INFO.:	US 1999-450310		19991129 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-462820, filed on 5 Jun 1995, now patented, Pat. No. US 5994392 Continuation of

Ser. No. US 1993-80675, filed on 21 Jun 1993, now abandoned Continuation of Ser. No. US 1992-952191, filed on 28 Sep 1992, now abandoned Continuation of Ser. No. US 1990-577329, filed on 4 Sep 1990, now abandoned Continuation-in-part of Ser. No. US 1990-535812, filed on 11 Jun 1990, now abandoned Continuation of Ser. No. US 1989-315134, filed on 24 Feb 1989, now patented, Pat. No. US 4933324 Continuation-in-part of Ser. No. US 1988-160667, filed on 26 Feb 1988, now patented, Pat. No. US 4939174

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Carr, Deborah
LEGAL REPRESENTATIVE: Wolf, Greenfield & Sacks, P.C.
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1410

DETD . . . muscle relaxants, anti-parkinson agents, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents, local anesthetics, anti-spasmodics and muscle contractants, prostaglandins, anti-bacterials, anti-septics, anti-depressants, anti-**migraine** preparations, central nervous system stimulants, imaging agents, specific targeting agents, proteins, peptides, anti-viral agents, anti-psychotic agents, anti-addiction agents and anti-emetics.

DETD . . . which produce a hypnotic effect. Hypnotics include pentobarbital sodium, phenobarbital, secobarbital, thiopental and mixtures, thereof, heterocyclic hypnotics, dioxopiperidines, glutarimides, diethyl **isovaleramide**, .alpha.-bromoisovaleryl urea, urethanes and disulfanes.

DETD Anti-**migraine** preparations are substances capable of preventing or relieving **migraine** headaches. Examples of such substances include. ergotamine tartrate, caffeine, dihydroengotamine mesylate propanolol HCl, acetominophin, and salicylic acid.

CLM What is claimed is:

. . . tranquilizer, anti-convulsant, muscle relaxant, anti-hypertensive agent, anti-pyretic agent, anti-inflammatory agent, local anesthetic, muscle contractant, prostaglandin, anti-bacterial agent, anti-septic agent, anti-depressant, anti-**migraine** agent, imaging agent, specific targeting agent, protein, anti-viral agent, anti-addition agent, or anti-emetic agent, wherein the compound is capable of. . .

33. The compound of claim 1, wherein the drug is an anti-**migraine** agent.

L10 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:300478 CAPLUS
DOCUMENT NUMBER: 134:316117
TITLE: Sustained-release formulations for treating CNS-mediated disorders
INVENTOR(S): Wells, David S.; Marriott, Thomas B.; Rajewski, Lian G.; Pipkin, James D.; Haslam, John L.
PATENT ASSIGNEE(S): Nps Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001028516	A2	20010426	WO 2000-US41267	20001019
WO 2001028516	A3	20020221		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2387819	AA	20010426	CA 2000-2387819	20001019
EP 1225888	A2	20020731	EP 2000-982701	20001019
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003512311	T2	20030402	JP 2001-531111	20001019
PRIORITY APPLN. INFO.:			US 1999-160210P	A2 19991019
			WO 2000-US41267	W 20001019

OTHER SOURCE(S): MARPAT 134:316117

AB Sustained-release compns. for delivering therapeutic concns. of **isovaleramide**, isovaleric acid, and certain structurally related compds. are provided for the treatment for a variety of pathol. conditions, including epilepsy and **spasticity**, which are ameliorated by effecting a modulation of CNS (central nervous system) activity. The ability of the compns. to sustain relatively const. levels of the drug at a therapeutic dose in the serum for extended periods of time enables a once or twice daily administration schedule. A film-coated tablet contg. **isovaleramide** (NPS 1776) 400, xanthan gum 56, lactose monohydrate 340, magnesium stearate 4, Aquacoate ECD 24.4, hydroxypropyl Me cellulose 9.8, di-Bu sebacate 5.8 mg was prepd.

IT **541-46-8, Isovaleramide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sustained-release formulations contg. isovalerate derivs. for treating CNS-mediated disorders)

L10 ANSWER 15 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2000:110003 USPATFULL
TITLE: Dopamine analog amide
INVENTOR(S): Shashoua, Victor E., Brookline, MA, United States
PATENT ASSIGNEE(S): Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6107499		20000822

APPLICATION INFO.: US 1995-466186 19950606 (8)
RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-80675, filed on 21 Jun
1993, now abandoned which is a continuation of Ser. No.
US 1992-952191, filed on 28 Sep 1992, now abandoned which is a continuation-in-part of Ser. No. US 1990-577329, filed on 4 Sep 1990, now abandoned which is a continuation-in-part of Ser. No. US 1990-535812, filed on 11 Jun 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-315134, filed on 24 Feb 1989, now patented, Pat. No. US 4933324 which
is a continuation-in-part of Ser. No. US 1988-160667, filed on 26 Feb 1988, now patented, Pat. No. US 4939174
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Carr, Deborah D
LEGAL REPRESENTATIVE: Wolf, Greenfield & Sacks P.C.
NUMBER OF CLAIMS: 43
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1438
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . muscle relaxants, anti-parkinson agents, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents, local anesthetics, anti-spasmodics and muscle contractants, prostaglandins, anti-bacterials, anti-septics, anti-depressants, anti-**migraine** preparations, central nervous system stimulants, imaging agents, specific targeting agents, proteins, peptides, anti-viral agents, anti-psychotic agents, anti-addiction agents and anti-emetics.
DETD . . . which produce a hypnotic effect. Hypnotics include pentobarbital sodium, phenobarbital, secobarbital, thiopental and mixtures, thereof, heterocyclic hypnotics, dioxopiperidines, glutarimides, diethyl **isovaleramide**, .alpha.-bromoisovaleryl urea, urethanes and disulfanes.
DETD Anti-**migraine** preparations are substances capable of preventing or relieving **migraine** headaches. Examples of such substances include ergotamine tartrate, caffeine, dihydroengotamine mesylate propanolol HCl, acetominophin, and salicylic acid.

L10 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:627974 CAPLUS
DOCUMENT NUMBER: 133:217710
TITLE: Treating a variety of pathological conditions, including **spasticity** and convulsions, by effecting modulation of CNS activity with **isovaleramide**, isovaleric acid, or a related compound
INVENTOR(S): Artman, Linda D.; Balandrin, Manuel; Smith, Robert L.
PATENT ASSIGNEE(S): NPS Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000051586	A2	20000908	WO 2000-US5324		20000301
WO 2000051586	A3	20011129			
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
US 6589994	B1	20030708	US 1999-258882		19990301
CA 2366038	AA	20000908	CA 2000-2366038		20000301
EP 1176953	A2	20020206	EP 2000-910383		20000301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002538106	T2	20021112	JP 2000-602054		20000301
PRIORITY APPLN. INFO.:			US 1999-258882	A	19990301
			US 1996-25050P	P	19960830
			WO 1997-US15272	A2	19970829
			WO 2000-US5324	W	20000301

OTHER SOURCE(S): MARPAT 133:217710

TI Treating a variety of pathological conditions, including **spasticity** and convulsions, by effecting modulation of CNS activity with **isovaleramide**, isovaleric acid, or a related compound

AB Prepns. and exts. of valerian, as well as **isovaleramide**, isovaleric acid, and certain structurally related compds. exhibit clin. significant pharmacol. properties which implicate a treatment for a variety of pathol. conditions, including **spasticity** and convulsions, which are ameliorated by effecting a modulation of CNS activity. The compns. in question generally are non-cytotoxic and do not elicit weakness or sedative activity at doses that are effective for the symptomatic treatment of such pathol. conditions.

ST **isovaleramide** isovalerate **spasticity** convulsion CNS modulation; isovaleric acid **spasticity** convulsion CNS modulation; valerian **spasticity** convulsion CNS modulation

IT Drugs of abuse
(abuse of; **isovaleramide**, isovaleric acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

IT Mental disorder
(affective; **isovaleramide**, isovaleric acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

IT Brain, disease
(amygdaloid kindling; **isovaleramide**, isovaleric acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

IT Valerianaceae
(and cramp bark and black haw; **isovaleramide**, isovaleric

acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

IT Anticonvulsants
Headache
Hop (Humulus)
Movement disorders
Nervous system agents
(**isovaleramide**, isovaleric acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

IT Mental disorder
(mood-affecting; **isovaleramide**, isovaleric acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

IT Analgesics
(neuropathic pain syndrome; **isovaleramide**, isovaleric acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

IT Nerve, disease
(neuropathy, neuropathic pain syndrome; **isovaleramide**, isovaleric acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

IT Cytoprotective agents
(neuroprotectants; **isovaleramide**, isovaleric acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

IT Mental disorder
(restlessness syndrome; **isovaleramide**, isovaleric acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

IT Nervous system
(**spasticity**; **isovaleramide**, isovaleric acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

IT 503-74-2, Isovaleric acid 503-74-2D, Isovaleric acid, esters and salts **541-46-8**, **Isovaleramide 541-46-8D**, **Isovaleramide**, derivs. 543-28-2, Isobutyl carbamate 926-04-5 1113-67-3 1746-77-6, Isopropyl carbamate 6968-27-0 19186-69-7 60199-80-6 61892-69-1 66309-91-9 88512-09-8 89854-87-5 89855-16-3 118873-18-0 241816-72-8 241816-73-9 241816-74-0 241816-75-1 241816-76-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**isovaleramide**, isovaleric acid, and related compds. for treatment of pathol. conditions, including **spasticity** and convulsions, by modulation of CNS activity)

L10 ANSWER 17 OF 18 USPATFULL on STN
ACCESSION NUMBER: 1999:155775 USPATFULL
TITLE: Antipsychotic prodrugs comprising an antipsychotic agent coupled to an unsaturated fatty acid
INVENTOR(S): Shashoua, Victor E., Brookline, MA, United States
PATENT ASSIGNEE(S): Neuromedica, Inc., Conshohocken, PA, United States

(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5994392		19991130
APPLICATION INFO.:	US 1995-462820		19950605 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-80675, filed on 21 Jun 1993, now abandoned which is a continuation of Ser. No. US 1992-952191, filed on 28 Sep 1992, now abandoned which is a continuation of Ser. No. US 1990-577329, filed on 4 Sep 1990, now abandoned which is a continuation-in-part of Ser. No. US 1990-535812, filed on 11 Jun 1990, now abandoned which is a continuation of Ser. No. US 1989-315134, filed on 24 Feb 1989, now patented, Pat. No. US 4933324 which is a continuation-in-part of Ser. No. US 1988-160667, filed on 26 Feb 1988, now patented, Pat. No. US 4939174

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Geist, Gary
ASSISTANT EXAMINER: Carr, Deborah D.
LEGAL REPRESENTATIVE: Wolf, Greenfield & Sacks, P.C.
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1475
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . muscle relaxants, anti-parkinson agents, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents, local anesthetics, anti-spasmodics and muscle contractants, prostaglandins, anti-bacterials, anti-septics, anti-depressants, anti-**migraine** preparations, central nervous system stimulants, imaging agents, specific targeting agents, proteins, peptides, anti-viral agents, anti-psychotic agents, anti-addiction agents and anti-emetics.

DETD . . . which produce a hypnotic effect. Hypnotics include pentobarbital sodium, phenobarbital, secobarbital, thiopental and mixtures, thereof, heterocyclic hypnotics, dioxopiperidines, glutarimides, diethyl **isovaleramide**, .alpha.-bromoisovaleryl urea, urethanes and disulfanes.

DETD Anti-**migraine** preparations are substances capable of preventing or relieving **migraine** headaches. Examples of such substances include ergotamine tartrate, caffeine, dihydroengotamine mesylate propanolol HCl, acetominophin, and salicylic acid.

L10 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:161122 CAPLUS
DOCUMENT NUMBER: 128:188636
TITLE: Treatment of **spasticity**, convulsions by isovaleric acid derivative CNS depressants
INVENTOR(S): Artman, Linda D.; Balandrin, Manuel F.
PATENT ASSIGNEE(S): NPS Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9808498	A1	19980305	WO 1997-US15272	19970829
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2264577	AA	19980305	CA 1997-2264577	19970829
AU 9743302	A1	19980319	AU 1997-43302	19970829
AU 728765	B2	20010118		
EP 938304	A1	19990901	EP 1997-941381	19970829
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9713188	A	19991103	BR 1997-13188	19970829
CN 1235541	A	19991117	CN 1997-199257	19970829
JP 2000504035	T2	20000404	JP 1998-511976	19970829
IL 128724	A1	20030529	IL 1997-128724	19970829
RU 2232016	C2	20040710	RU 1999-106406	19970829
US 6589994	B1	20030708	US 1999-258882	19990301
KR 2000038194	A	20000705	KR 1999-701716	19990302
US 2004072900	A1	20040415	US 2003-614344	20030708
PRIORITY APPLN. INFO.:			US 1996-25050P	P 19960830
			WO 1997-US15272	W 19970829
			US 1999-258882	A3 19990301

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Treatment of **spasticity**, convulsions by isovaleric acid derivative CNS depressants

AB Prepns. and exts. of valerian, as well as **isovaleramide**, isovaleric acid, and its pharmaceutically acceptable salts, esters, and substituted amides, exhibit clin. significant pharmacol. properties which implicate a treatment for a variety of pathol. conditions, including **spasticity** and convulsions, which are ameliorated by effecting a mild depression of CNS activity. The compns. in question generally are non-cytotoxic and do not elicit weakness or sedative activity at doses that are effective for the symptomatic treatment of such pathol. conditions.

ST isovalerate deriv CNS depressant **spasticity** convulsion; valerian ext CNS depressant **spasticity** convulsion; **isovaleramide** CNS depressant **spasticity** convulsion

IT Mental disorder
(affective; isovaleric acid and derivs. for treatment of **spasticity** and convulsions)

IT Viburnum
(black haw, ext.; isovaleric acid and derivs. for treatment of **spasticity** and convulsions)

IT Bark

(cramp, ext.; isovaleric acid and derivs. for treatment of **spasticity** and convulsions)
IT Hop (Humulus)
Valerianaceae
(ext.; isovaleric acid and derivs. for treatment of **spasticity** and convulsions)
IT Analgesics
(for central neuropathic pain syndrome; isovaleric acid and derivs. for
treatment of **spasticity** and convulsions)
IT Spinal cord
(injury, **spasticity** assocd. with; isovaleric acid and derivs. for treatment of **spasticity** and convulsions)
IT Anticonvulsants
Drug delivery systems
Headache
Nervous system depressants
Valerian (Valeriana)
(isovaleric acid and derivs. for treatment of **spasticity** and convulsions)
IT Mental disorder
(mood-affecting; isovaleric acid and derivs. for treatment of **spasticity** and convulsions)
IT Disease, animal
(restlessness syndrome; isovaleric acid and derivs. for treatment of **spasticity** and convulsions)
IT Muscle relaxants
(spasmolytics; isovaleric acid and derivs. for treatment of **spasticity** and convulsions)
IT Multiple sclerosis
(**spasticity** assocd. with; isovaleric acid and derivs. for treatment of **spasticity** and convulsions)
IT Nervous system
(**spasticity**; isovaleric acid and derivs. for treatment of **spasticity** and convulsions)
IT Muscle
(tone; isovaleric acid and derivs. for treatment of **spasticity** and convulsions)
IT 503-74-2, Isovaleric acid 503-74-2D, Isovaleric acid, esters and amides and salts **541-46-8, Isovaleramide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(isovaleric acid and derivs. for treatment of **spasticity** and convulsions)

=> d his

(FILE 'HOME' ENTERED AT 12:34:45 ON 10 DEC 2004)

FILE 'REGISTRY' ENTERED AT 12:35:02 ON 10 DEC 2004
L1 1 S ISOVALERAMIDE/CN

FILE 'USPATFULL, CAPLUS, EMBASE' ENTERED AT 12:35:14 ON 10 DEC 2004
E CONVULSION/CT

```
L2         22119 S E3 OR COVULSION#
                 E SPASTICITY
                 E SPASTICITY/CT
L3          9155 S E3-E12 OR SPASTICITY
                 E HEADACHES/CT
                 E HEADACHE/CT
L4         94363 S E3-E12 OR HEADACHE OR MIGRAINE
                 E MIGRAINE/CT
L5         15187 S E3-E12
L6           364 S L1 OR ISOVALERAMIDE
L7        123792 S L2 OR L3 OR L4 OR L5
L8            20 S L6 (25W) L7
L9            20 S L6 AND L7
L10           18 DUPLICATE REMOVE L9 (2 DUPLICATES REMOVED)

=> log hold
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   117.32     122.38

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -2.80      -2.80

 SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 12:39:03 ON 10 DEC 2004
1
```